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Mortality in Hematologic Malignancy and Hematopoietic Stem Cell Transplant Patients with Mucormycosis, 2001 to 2009▽

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Mortality due to mucormycosis is high. We assessed clinical characteristics and mortality among stem cell transplant and hematologic malignancy patients diagnosed with mucormycosis from 2001 to 2009. Thirty patients were diagnosed with probable or proven mucormycosis during the study. Twenty-six were diagnosed premortem, and most were treated with liposomal amphotericin B single-agent antifungal therapy initially. While the initial antifungal and surgical treatment approach remained stable throughout the study period, 6-week mortality significantly declined over time (67% in 2001 to 2003 versus 45% in 2004 to 2006 versus 20% in 2007 to 2009 [$P = 0.04$]), as did 12-week mortality (78% in 2001 to 2003 versus 55% in 2004 to 2006 versus 20% in 2007 to 2009 [$P = 0.01$]).

Mucormycosis is associated with substantial morbidity and mortality, particularly among oncology patients (10, 12). In a review of mucormycosis reported between 1940 and 2003, mortality rates in patients with cancer and in hematopoietic stem cell transplant (HSCT) recipients were 66% and 91%, respectively (12).

Historically, treatment of mucormycosis has been challenging due to limited treatment options. Amphotericin B deoxycholate (AmB) remains the only drug approved for treatment. However, given the drug toxicities associated with AmB, lipid formulations of AmB are often used instead (5, 14). Furthermore, posaconazole, which has significant clinical efficacy against Mucorales, has become available (3, 16). In addition, new therapeutic strategies against Mucorales have been proposed recently, including use of caspofungin in combination with amphotericin-based therapy and adjunctive use of deferasirox in combination with antifungal therapy (11, 15).

The efficacy of new therapeutic options and their impact on mortality in patients with mucormycosis remain unclear. One recent Italian multicenter retrospective study suggests that even in the absence of new therapeutic approaches, mortality from mucormycosis is declining. Those authors reported a significant decline in attributable mortality in patients treated for mucormycosis between 1987 and 1993 versus between 2004 and 2007, from 70% to 40% (10).

In order to assess temporal trends in mortality and clinical characteristics associated with mucormycosis, we retrospectively studied all HSCT recipients or patients with hematologic malignancy (HM) diagnosed with mucormycosis at our institution, where the standard initial management of mucormycosis is surgical assessment and liposomal amphotericin B (LAmB) monotherapy.

(This work was presented in abstract form at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 13 September 2009 [4a].)

MATERIALS AND METHODS

Patients. All adult HSCT and HM patients diagnosed with mucormycosis at Dana-Farber Cancer Institute/Brigham and Women's Hospital (DFCI/BWH) between 1 January 2001 and 31 December 2009 were included in this analysis. Follow-up concluded on 1 May 2010. The Office for Human Research Studies at the DFCI/BWH approved this study.

Medical records were reviewed for covariates of interest, including gender, age, underlying HM, reason for HSCT, type of HSCT, diabetes mellitus, glycosylated hemoglobin, iron overload, medications used to treat iron overload, significant use of corticosteroids and voriconazole prior to mucormycosis, absolute neutrophil count at mucormycosis diagnosis, duration of neutropenia, site of infection, species (where cultures grew), timing and agent of antifungal therapy, presence of other infections, and survival.

Corticosteroid use was considered significant if >0.3 mg/kg prednisone daily (or steroid equivalent) was administered >21 days before mucormycosis diagnosis (2). Voriconazole use was considered significant if administered for >20 days within 1 month of diagnosis (8). Neutropenia was defined as an absolute neutrophil count of <500 cells per microliter. Survival was assessed at 6 weeks and 12 weeks after diagnosis of mucormycosis as proposed by Segal and colleagues (13).

Mucormycosis. Mucormycosis diagnostic certainty was defined by European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) criteria; only proven or probable cases were included (2). Tissue specimens in proven cases were reviewed by an anatomic pathologist at the time of collection, and all available specimens were reviewed again by an infectious diseases pathologist when this study was undertaken. Standard fungal cultures were performed on all tissue and other specimens, and in cases where culture yielded growth of a fungus, isolated fungi were identified by standard phenotypic methods. Species identification was confirmed for most isolates by phenotypic methods at a national reference laboratory (Fungus Testing Laboratory, University of Texas Health Science Center, San Antonio, TX). Mucormycosis was further confirmed by PCR targeting 18S ribosomal DNA of Mucorales on formalin-fixed paraffin-embedded tissue samples in 22 of 28 proven cases as described elsewhere (4).

The standard approach to HM and HSCT patients with suspected fungal infection at DFCI/BWH includes computed tomography and measurement of serum fungal antigens, including galactomannan (Platelia Aspergillus enzyme immunoassay; Bio-Rad Laboratories Inc., Hercules, CA) and (1→3)-β-D-glucan (Fungitell assay; Associates of Cape Cod, Inc., East Falmouth, MA), which became available at DFCI/BWH in 2003 and 2004, respectively. Mucormycosis onset was captured at the time of clinical suspicion, based on radiographic findings and initiation of empirical treatment. Infection was considered disseminated if there was evidence of infection in two or more noncontiguous anatomic sites.

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Management of mucormycosis at DFCI/BWH includes surgical assessment for debridement where appropriate and single-agent antifungal therapy. Specifically, monotherapy with LAmB (5 mg/kg intravenously daily) is the preferred treatment, but occasionally AmB (1 mg/kg intravenously daily) or posaconazole (200 mg orally every 6 h) was used, depending upon renal function and comorbidities. Posaconazole became available as an expanded-access investigational drug at DFCI/BWH in 2003 (3, 16).

Statistical analysis. Categorical patient characteristics by triennia of diagnosis were compared by the Mantel-Haenszel trend test. Continuous patient characteristics by triennia of diagnosis were compared by the Kruskal-Wallis test. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Mucormycosis was diagnosed in 30 HM and HSCT patients at DFCI/BWH between 2001 and 2009, including 28 proven and 2 probable cases. Diagnosis was confirmed by autopsy in 5 cases, tissue biopsy in 20 cases, tissue fine-needle aspiration in 3 cases, and respiratory cultures in the setting of appropriate radiographic findings and host factors in 2 cases.

Clinical characteristics are listed in Table 1. There were similar numbers of HM and HCST patients. Ten HM patients had acute myelogenous leukemia or myelodysplastic syndrome, two had acute lymphoblastic leukemia, and two had plasma cell dyscrasia. The majority of HSCT recipients underwent allogeneic transplantation (14/16). Twelve patients had disseminated mucormycosis, and 18 had local infection, including 8 pulmonary, 8 sino-orbital, and 2 cutaneous infections. Thirteen patients underwent at least one surgical debridement or excision. The median time to debridement or surgical excision was 5 days from clinical diagnosis of mucormycosis (range, 1 to 94 days). Six-week all-cause mortality after clinical diagnosis of mucormycosis was 43% (13/30), and 12-week all-cause mortality was 50% (15/30).

Temporal trends in clinical characteristics, 6-week mortality, and 12-week mortality were assessed by triennia (Table 1). There was a significant decline in 6-week mortality (67% in 2001 to 2003 versus 45% in 2004 to 2006 versus 20% in 2007 to 2009 [$P = 0.04$]) and in 12-week mortality (78% in 2001 to 2003 versus 55% in 2004 to 2006 versus 20% in 2007 to 2009 [$P = 0.01$]). Concomitantly, there was a significant trend toward more HM patients with mucormycosis, more neutropenia at diagnosis, and fewer patients treated with corticosteroids or voriconazole before diagnosis. There were no significant trends in the proportions of men, patients with active malignancy, patients with diabetes mellitus, disseminated infection, patients cared for in the intensive care unit at the time of diagnosis, surgical debridement, or treatment within 6 days of diagnosis by triennia over the course of the study. Among the patients with localized infection limited to the sinuses or pulmonary system, there was no significant trend in those with pulmonary versus sinus infection. In addition, among those patients who were neutropenic at diagnosis of mucormycosis, there were no significant differences in the overall duration of neutropenia or the duration from diagnosis of mucormycosis to the resolution of neutropenia by triennia.

Temporal trends in transplant characteristics among the 14 allogeneic HSCT recipients were also assessed by triennia (Table 2). As the number of patients who had undergone an allogeneic HSCT declined significantly over time (only one patient in the most recent triennium had undergone allogeneic HSCT), it is difficult to draw conclusions about the impact of specific transplant-related characteristics such as donor and recipient cytomegalovirus (CMV) status and donor human leukocyte antigen matching on 6- and 12-week mortality.

The presence of concomitant infections among patients in the cohort was assessed. Four patients (13%) had CMV viremia within 1 month of the diagnosis of mucormycosis, including two patients diagnosed during the first triennium and one each diagnosed during the second and third triennia. All were treated with antiviral therapy such that CMV was undetectable by blood PCR or hybrid capture testing at the time mucormycosis was clinically diagnosed. Three of four were allogeneic HSCT recipients, and one had been treated with alemtuzumab for refractory acute lymphoblastic leukemia. One patient with CMV infection prior to the diagnosis of mucormycosis was also diagnosed with *Pneumocystis jirovecii* pneumonia and adenovirus infection of the gastrointestinal tract within days of the diagnosis of mucormycosis. Three other patients had bacterial infections within 1 week of the diagnosis of mucormycosis, including two patients with *Enterococcus faecium* bacteremia and one with *Escherichia coli* bacterial superinfection of pulmonary *Rhizopus* species infection.

Two patients in the cohort were formally diagnosed with iron overload and were actively being treated with iron chelation at the time mucormycosis was diagnosed; one patient, diagnosed between 2001 and 2003, was being treated with deferoxamine, and the other, diagnosed between 2007 and 2009, was being treated with deferasirox.

Among the eight patients in the cohort with diabetes mellitus or glucose intolerance, none had glucose measurements persistently above 300 mg per deciliter. Four patients had glycosylated hemoglobin measurements within a month of the diagnosis of mucormycosis; the range in measurements was 6.6 to 8.1% (median, 7.0%).

Tissue or respiratory cultures grew Mucorales in 15 cases. Six infections were due to *Rhizopus* species, three to *Cunninghamella* species, three to *Mucor* species, two to *Rhizomucor* species, and one to *Lichtheimia* (syn. *Absidia* pro parte) species. Among 15 culture-negative cases, Mucorales PCR and sequencing resulted in genus identification in 12, including four due to *Rhizopus* species, four to *Cunninghamella* species, three to *Rhizomucor* species, and one to *Lichtheimia* species (4). There was no difference in 6-week mortality based on the identified genus for patients with positive cultures or for those with negative cultures in whom the genus was identified by PCR.

The first effective antifungal given after diagnosis of mucormycosis was LAmB in 21 patients, AmB in one, and posaconazole in three. Fourteen of 22 patients initially treated with LAmB or AmB later switched to posaconazole due to toxicity or for oral outpatient antifungal therapy at a median of 14.5 days (range, 1 to 39 days). Five patients were not treated, including four diagnosed at autopsy and one who elected not to pursue aggressive care after mucormycosis was diagnosed.

DISCUSSION

These data demonstrate a significant trend toward improved 6-week and 12-week survival between 2001 and 2009 in this cohort of HM and HSCT patients with proven or probable mucormycosis. Notably, 6-week and 12-week mortality in HM

TABLE 1. Characteristics of mucormycosis by triennia

Characteristic[a]	2001–2003	2004–2006	2007–2009	Total	*P*
No. of cases	9	11	10	30	
Median age at diagnosis, yr (range)	53 (34–74)	48 (22–78)	61 (24–83)	54 (22–83)	0.23
Gender					0.08
Male	8 (89)	7 (64)	5 (50)	20 (67)	
Female	1 (11)	4 (36)	5 (50)	10 (33)	
Underlying condition					0.0007
HSCT[b]	8 (89)	7 (64)	1 (10)	16 (53)	
HM[c]	1 (11)	4 (36)	9 (90)	14 (47)	
Oncologic status					0.27
Active malignancy	4 (44)	6 (55)	7 (70)	17 (57)	
Remission	5 (56)	5 (45)	3 (30)	13 (43)	
Neutropenia at diagnosis					0.002
Yes	0 (0)	5 (45)	7 (70)	12 (40)	
No	9 (100)	6 (55)	3 (30)	18 (60)	
Median duration of neutropenia ($n = 12$), days (range)		25 (12–54)	24 (12–48)	25 (12–54)	0.74
Median duration of neutrophil recovery ($n = 12$), days (range)		10 (5–11)	6 (3–28)	7 (3–28)	0.68
Diabetes or glucose intolerance					0.52
Yes	4 (44)	1 (9)	3 (30)	8 (27)	
No	5 (56)	10 (91)	7 (70)	22 (73)	
Steroids prior to diagnosis					0.0006
Yes	8 (89)	3 (27)	1 (10)	12 (40)	
No	1 (11)	8 (73)	9 (90)	18 (60)	
Voriconazole prior to diagnosis					0.01
Yes	4 (44)	1 (9)	0 (0)	5 (17)	
No	5 (55)	10 (91)	10 (100)	25 (83)	
Site of Infection					0.12
Localized[d]	3 (33)	8 (73)	7 (70)	18 (60)	
Disseminated	6 (67)	3 (27)	3 (30)	12 (40)	
Site of localized infection ($n = 16$)[e]					0.20
Sinus	2 (67)	4 (67)	2 (29)	8 (50)	
Pulmonary	1 (33)	2 (33)	5 (71)	8 (50)	
Care in an intensive care unit[f]					0.52
Yes	4 (44)	3 (27)	3 (30)	10 (33)	
No	5 (56)	8 (73)	7 (70)	20 (67)	
Surgical debridement					0.80
Yes	2 (22)	8 (73)	3 (30)	13 (43)	
No	7 (78)	3 (27)	7 (70)	17 (57)	
Initiation of therapy within 6 days[g]					0.63
Yes	3 (50)	9 (90)	6 (67)	18 (72)	
No	3 (50)	1 (10)	3 (33)	7 (28)	
6-week outcome					0.04
Dead	6 (67)	5 (45)	2 (20)	13 (43)	
Survived	3 (33)	6 (55)	8 (80)	17 (57)	
12-week outcome					0.01
Dead	7 (78)	6 (55)	2 (20)	15 (50)	
Survived	2 (22)	5 (45)	8 (80)	15 (50)	

[a] Unless otherwise indicated, values are the number (percentage) of patients.
[b] Fourteen allogeneic HSCT recipients and 2 autologous HSCT recipients.
[c] Ten patients with acute myelogenous leukemia and/or myelodysplastic syndrome, 2 with acute lymphoblastic leukemia, and 2 with plasma cell dyscrasia.
[d] Eight pulmonary, 8 sino-orbital, 2 cutaneous.
[e] Excluding the two patients with infection limited to skin.
[f] Intensive care unit-level care within 1 week of the clinical diagnosis of mucormycosis.
[g] Excludes 4 patients who were diagnosed with mucormycosis at autopsy and 1 patient who chose comfort care at clinical diagnosis and thus was never treated. Twenty-two patients were treated with liposomal amphotericin, 1 patient was treated with amphotericin B deoxycholate, and 3 patients were treated with posaconazole.

and HSCT patients with proven or probable mucormycosis diagnosed between 2007 and 2009 was 20%, which is lower than has been reported in other studies.

Though posaconazole was not available during the first 2 years of study, initial treatment practices at DFCI/BWH were otherwise stable, with the majority of patients receiving initial antifungal therapy with LAmB; thus, changes in antifungal treatment practice exclusively do not explain improved survival, though they may have contributed to reduced medication-related toxicity. In addition, the temporal rise in 6-week and 12-week survival was not clearly related to a decline in risk factors reported in other studies, including lack of debridement or delay in initiating antifungal therapy (1, 10). Diagnostic practices for suspected invasive fungal infections changed during the study period when galactomannan and (1→3)-beta-D-glucan assays became available in 2003 and 2004. While

TABLE 2. Characteristics of mucormycosis in allogeneic hematopoietic stem cell transplant recipients

Characteristic[a]	2001–2003	2004–2006	2007–2009	Total
No. of cases	8	5	1	14
HLA match[b]				
Matched donor	8 (100)	2 (40)	1 (100)	11 (79)
Mismatched donor[c]	0 (0)	3 (60)	0 (0)	3 (21)
Donor relatedness				
Related donor	2 (25)	1 (20)	1 (100)	4 (29)
Unrelated donor	6 (75)	4 (80)	0 (0)	10 (71)
CMV status				
Donor −/recipient −	2 (25)	4 (80)	1 (100)	7 (50)
Donor +/recipient −	3 (38)	1 (20)	0 (0)	4 (29)
Donor +/recipient +	2 (25)	0 (0)	0 (0)	2 (14)
Donor −/recipient +	1 (13)	0 (0)	0 (0)	1 (7)
GVHD				
Yes[d]	6 (75)	2 (40)	0 (0)	8 (57)
No	2 (25)	3 (60)	1 (100)	6 (43)

[a] Values are the number (percentage) of patients.
[b] Donors were considered HLA matched if 6/6 HLA A, B, and DRB1 were identical.
[c] Includes two recipients of umbilical cord blood stem cells from two donors and one recipient of a 5/6 human leukocyte antigen-matched donor.
[d] Includes 3 patients with acute graft-versus-host disease (GVHD) (1 each of grades 2, 3, and 4) and 5 patients with chronic GVHD, all of whom had limited disease.

neither the galactomannan nor the (1→3)-beta-D-glucan assay is helpful in diagnosing mucormycosis, these assays can aid in the diagnosis of other invasive fungal infections such as aspergillosis, thus allowing for more targeted use of invasive diagnostic procedures such as biopsy in cases of suspected invasive fungal infection where galactomannan and (1→3)-beta-D-glucan assay results are negative. Nonetheless, despite these advances in fungal diagnostics, the number of patients diagnosed with mucormycosis by triennia during the study did not change.

Our analysis revealed that the type of patient developing mucormycosis at our center has changed over 9 years from mostly HSCT recipients to mostly HM patients. Concomitantly, more patients are neutropenic and fewer are on corticosteroids or voriconazole at diagnosis. Typically, allogeneic HSCT patients diagnosed with mucormycosis during the study period were being treated with corticosteroids for severe graft-versus-host disease and with voriconazole for prevention of invasive fungal disease at diagnosis (6, 8). In contrast, HM patients diagnosed during the study were often neutropenic at diagnosis.

A potential explanation for the shift toward diagnosis of mucormycosis in neutropenic HM patients is a change in febrile neutropenia treatment practices at our center. When caspofungin was approved for empirical treatment of prolonged febrile neutropenia in 2004, echinocandin displaced LAmB as the preferred agent for this indication at DFCI/BWH. Thus, HM patients with prolonged febrile neutropenia after 2004 were less often exposed to LAmB prior to mucormycosis diagnosis and may therefore have been more susceptible to developing clinically significant mucormycosis. Notably, other studies have reported that neutropenia recovery is associated with improved survival (1, 9); thus, the shift toward mucormycosis in neutropenic HM patients (who typically recover from neutropenia) in our cohort may, in part, explain the observed trend.

Another potential explanation for the improved survival in the more recent patients in our cohort, who were less likely to be on voriconazole at the time of mucormycosis diagnosis, is that the virulence of Mucorales previously exposed to voriconazole may be increased, as has been suggested by murine and fly studies (7).

In conclusion, analysis of mucormycosis in HM and HSCT patients at DFCI/BWH between 2001 and 2009 revealed a significant decline in 6-week and 12-week mortality despite stable treatment practices, which included initial monotherapy with LAmB. While the present study is limited by the relatively small sample size, which precludes a more detailed multivariate analysis, the clear trend in both 6-week and 12-week mortality is an important consideration when interpreting studies of new mucormycosis treatments in which a single treatment arm or historical controls are used.

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